Type 2 Diabetes Mellitus: The Grand Overview

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Type 2 diabetes currently accounts for over 100 billion dollars in annual healthcare expenditure in the United States and 28 % of the national (Medicare) healthcare budget for elderly Americans. In our inner-city hospital, 20 % of all 950 beds are occupied by patients with diabetes; and 28–38 % of patients receiving cardiac care in Coronary Care Units, catheterization laboratories or cardiovascular surgery, have diabetes as an underlying disorder. Both computer modelling and controlled clinical trials suggest that intensive therapy of diabetes can reduce significantly the morbidity and costs associated with this increasingly common disorder. Early detection of carbohydrate intolerance holds great promise for preventing the onset, progression and complications of Type 2 diabetes. To date our efforts have been futile, with 20 % of newly diagnosed Type 2 diabetic patients already complicated by retinopathy and 14 % complicated by peripheral vascular disease. It is now clear that high-risk individuals can be identified, and intervention trials are underway to test the hypothesis that Type 2 diabetes (and its attendant cardiovascular risks) can be prevented. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) in Canada and Europe has randomized 1200 individuals with impaired glucose tolerance (IGT) into a three-year trial to prevent disease progression. The Diabetes Prevention Program (DPP) in the US has randomized almost 3000 individuals with IGT into a six-year, three-arm study testing the efficacy of intensive lifestyle and pharmacological therapy in disease progression. Together, these studies should provide a public health model for the recognition of high-risk individuals and interventions to stem the epidemic of Type 2 diabetes. For those patients suffering with Type 2 diabetes already, pancreas transplantation remains an extreme intervention with the potential for 'curing' diabetes. Although applied usually to patients with Type 1 diabetes, experience is accumulating of transplantation in Type 2 diabetic patients with end-stage renal disease. Outcomes for these individuals are as good as for Type 1 diabetes. Islet-cell transplants, in fact, have been more successful in Type 2 diabetes compared with Type 1. Improved islet-cell availability, better immunosuppression, and the possibility of antigen masking make this technology a major hope for the future.

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Introduction

Type 2 diabetes currently accounts for over US $100 billion in annual healthcare expenditure in the USA[1] and 28 % of the national (Medicare) healthcare budget for elderly Americans.[2] Almost 20 % of Americans over the age of 65 have diabetes, which is predicted to increase to over 30 % by the year 2010.[2] This epidemic requires a societal examination of disease risk and intervention efforts to prevent and cure diabetes.

When an individual with diabetes presents to a physician, two questions are typically on their minds: firstly, 'why did I develop diabetes and how could I have possibly avoided it?'; and secondly, 'how can you cure me?' Although we are still at a loss to explain the complete pathophysiology and pathogenesis of Type 2 diabetes at the molecular level, epidemiological studies provide us with adequate guidelines for identifying the individuals at highest risk for its development. Biochemical criteria remain the best predictors for the future development of Type 2 diabetes. The presence of diabetes during pregnancy yields a 33 % probability of developing Type 2 diabetes in the 5-year period after childbirth.[3] In addition, impaired glucose tolerance (IGT) develops into Type 2 diabetes at a rate of approximately 7 % per year, depending on the ethnic group.[4] Historical and anthropometric features are used to identify patients at risk who may then undergo biochemical assessment for disease. Family history of diabetes, being a member of an ethnic minority, obesity, age >65 years and simultaneous presence of hypertension and/or hypertriglyceridaemia make the possibility of IGT greater. In the USA, 11 % of the adult population has IGT; this figure increases to 18 % in people over the age of 65.[2]

Identification of those individuals at highest risk of developing diabetes allows the introduction of interventions that may delay or prevent the progression

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of diabetes. Interventions designed to reduce insulin resistance and protect the β-cell from failure could theoretically prevent or delay the progression to Type 2 diabetes. Such interventions have now been integrated into a variety of controlled prospective clinical trials designed for this purpose (Table 1). Results from the Da Qing study in China showed the effectiveness of a lifestyle intervention, which prevents progression of carbohydrate intolerance.[5] The comparability of this study to other populations has, however, been questioned. Both the Diabetes Prevention Program and Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) trials in Europe hope to expand on this experience.

The use of acarbose to control postprandial glycaemic excursion, and thus protect the β-cell, is currently being utilized in the STOP NIDDM study. This protocol has randomized 1200 into either a placebo- or acarbose-treated regimen to be followed over a 3-year period for progression to diabetes, as well as cardiovascular risk factors.

The largest prospective study investigating the prevention or delay of Type 2 diabetes is the Diabetes Prevention Program now underway in the USA. To date, almost 3000 participants have been randomized. These individuals are in the upper 50th percentile of IGT with fasting glucose levels ranging from 5.2–7.0 $mmol \cdot l^{-1}$. At this point in time, 36 % of the subjects are male, 11 % are over the age of 65 years and ethnic minority participants account for 44 % of the total randomized population. Participants are randomized to one of three groups: a single unblinded group consisting of an intensive lifestyle intervention, which aims for a 7 % weight loss together with an increased expenditure of 700 kcal per week to be achieved in the first 6 months and maintained for the duration of the study; and two further randomized groups who receive standard lifestyle recommendations including caloric restriction, modification of fat intake and increase in caloric expenditure. Furthermore, these groups receive either a placebo or active medication designed to improve insulin sensitivity. The study was initially designed as a four-arm trial, comparing troglitazone, metformin and intensive lifestyle modification with a placebo-treated control group. After 22 months of recruitment and randomization of over 2000 participants, the troglitazone treatment was withdrawn from the study. A death in this group from liver failure and complications of liver transplantation suggested an unacceptable risk–benefit assessment for a primary prevention trial. The other three groups continue to have subjects randomized into them, while the troglitazone treated participants were unmasked to treatment and will continue to be followed for observational analysis.

With an average follow up of 4.5 years, the study group hopes to demonstrate delay or prevention of the development of Type 2 diabetes, as well as the reduction of risk factors associated with cardiovascular disease. Although the study is not adequately powered to demonstrate differences in cardiovascular events, carotid artery wall thickness is being evaluated prospectively as a surrogate measure. Ancillary trials are examining the effects of changes in distribution of fat as well as specific measures of insulin resistance.

Although prevention strategies are the best hope for stemming the epidemic of Type 2 diabetes, they are of limited value in aiding those patients already afflicted with the disease (Table 2). The United Kingdom Prospective Diabetes Study (UKPDS) has clearly demonstrated that Type 2 diabetes is a progressive disease with consistent deterioration in glycaemic control over time, which demands increased pharmacological intervention.[6] In time, at least 33 % of individuals ultimately require insulin therapy to manage their hyperglycaemia. The ability to deliver insulin in a physiological manner is limited by current insulin preparations and the means by which insulin is administered. With the development of insulin analogues, we can administer insulin in a manner that is closer to normal physiological delivery. However, most patients would consider this technology to be rather primitive because it continues to require subcutaneous injections, self-monitoring of blood glucose and the determination of the appropriate quantity of insulin to take based on diet, exercise and glucose measurements.

The development of a closed-loop insulin infusion system has clearly been limited by the availability of a reliable, long-acting glucose sensor. To date, no implantable or invasive methods (Table 3) have been shown to work effectively beyond 96 hours.[7] However, an implantable insulin-infusion system will deliver intraportal insulin in a near-normal physiological manner. These systems have demonstrated some degree of success and may be more effective than multiple daily insulin injections in the treatment of Type 2 diabetes (Table 4).[8]

The ultimate 'cure' for Type 2 diabetes remains the implantation of functioning β-cells that are capable of overcoming the inherent insulin resistance of the con-

Table 1. Type 2 diabetes prevention studies

Lifestyle modifications

- Da Qing
- Diabetes Prevention Study

Pharmacological therapy

- Malmo
- Diabetes Primary Prevention
- Study to Prevent Non-Insulin-Dependent Diabetes Mellitus

Table 2. Cures for diabetes

- Closed-loop insulin infusion system
- Pancreas transplants
- Islet-cell transplants

Table 3. Currently available glucose sensors

In vivo glucose sensors	
Implantable sensors	Non-invasive sensors
• Enzyme electrodes	• Near-infrared spectroscopy
• Optical sensors	• Photoacoustic spectroscopy
• Microdialysis systems	• Light scattering
	• Reverse ionophoresis

dition and maintaining normal glycaemia. Although the American Diabetes Association technical review has suggested that pancreas transplantation should be limited to individuals with Type 1 diabetes,[9] increasing evidence is demonstrating the efficacy of pancreas transplantation in the treatment of Type 2 diabetes. When combined with kidney transplantation, pancreas transplantation in patients with Type 2 diabetes complicated by end-stage renal disease results in outcomes as successful, if not better, than in those patients with Type 1 diabetes. Patient survival at 3 years exceeds 90 %, with graft survival and insulin independence being achieved in more than 75 % of patients at 3 years.[10] These studies clearly show the ability of genetically distinct β-cells to overcome the endogenous insulin resistance of Type 2 diabetes, as well as the resistance imposed by glucocorticoid and immunosuppressive therapy.

Whole pancreas transplants, however, are currently limited to individuals who would otherwise require immunosuppressive therapy for a renal transplant. Objectives for the future include the provision of β-cells that function in a transplant setting before the need for a kidney transplant. Genetically modified islets or xenotransplants could potentially serve this purpose and hopefully could be used in the absence of systemic immunosuppression to the recipient. The use of bio-hybrid devices in which micro-encapsulation allows glucose and insulin to move freely, but prevents immune recognition, has been actively studied for 20 years.[11] Antigen masking through genetic engineering or *in vitro* exposure also has excellent potential because it can modify the donor cells and preclude the need for immunosuppression in the recipient.[12]

Finally, genetic engineering to create new insulin-secreting cells may obviate the autoimmunity problems associated with Type 1 diabetes and augment the relative insulin deficiency noted in Type 2 diabetes. Introducing the capacity to manufacture and secrete human insulin is insufficient for a cell to mimic the function of the β-cell. Feedback control of insulin secretion by ambient glucose is required for the appropriate function of this artificial β-cell. Both hepatic and anterior pituitary-derived cells have been modified with the introduction of cDNA for insulin and GLUT-2, the putative islet cell glucose sensor.[13] Problems persist in linking these two critical β-cell functions but gene therapy provides another unique avenue for the cure of diabetes.[14]

Pharmacological developments over the past 10 years have provided innovative approaches to the treatment of patients with Type 2 diabetes, which have resulted in improved glycaemic control and reduction in cardiovascular risk factors. Future strategies must centre around preventing new cases of diabetes to control a potential epidemic and the possibility of a cure for those patients already afflicted.

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Table 4. Implantable infusion pumps vs. multiple-dose injections in Type 2 diabetes

	Multiple-dose injections (n = 52)	Implantable infusion pumps (n = 59)
Mean fasting glucose		
Baseline (mg·dl^{-1})	176 ± 69.3	164 ± 45.6
End of study (mg·dl^{-1})	164 ± 36.2	148 ± 27.3
Mean HbA_{1c}		
Baseline (%)	8.85 ± 1.3	8.77 ± 1.2
End of study (%)	7.54 ± 0.8	7.34 ± 0.8
Change in daily insulin dose (U·day^{-1})	12 ± 19.9	5.4 ± 31.5
Change in body weight (kg)	+0.36	−0.99*

*P = 0.01; adapted from Saudek *et al*. 1996.[8]

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